UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,447	04/22/2005	Aldo Pinchera	B-0496 PUS	1713

31834 7590 06/14/2010

BRACCO RESEARCH USA INC.
305- COLLEGE ROAD EAST
PRINCETON, NJ 08540

EXAMINER	
KLINKEL, KORTNEY L	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
06/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,447	PINCHERA ET AL.	
	Examiner	Art Unit	
	Kortney L. Klinkel	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/2010 has been entered.

Claims 1-8 and 16 stand canceled. Claims 9, 14, 17, and 20 were amended. Claims 17-24 remain withdrawn for being directed to a non-elected invention. Claims 9-15 and 17-25 are pending and claims 9-15 and 25 are under consideration in the instant Office action.

Claim Rejections - 35 USC § 103—Withdrawn

The rejection of claims 9-15 and 25 under 35 U.S.C. 103(a) as being unpatentable over Santini et al. Thyromimetic effects of 3,5,-3'-triiodothyronine sulfate in hypothyroid rats. Endocrinology. 1993;133(1): 105-110; already made of record by applicant), in view of Miura et al. (US Patent 5,116,828; already made of record) is withdrawn in light of a stronger rejection presented below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-10, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Chopra et al. ("Demonstration of Thyromimetic Effects of 3,5,3'-Triiodothyronine Sulfate (T_3S) in Euthyroid Rats" Thyroid, 1996, 6(3), 229-232, as per Applicant's IDS dated 4/22/2005).

Chopra et al. teach a liquid composition comprising triiodothyronine sulfate (T_3S) in a dose of 3.5 μg, 10.5 μg and 31.5 μg (p. 230, Experimental procedures). Note that the dosage amount of 31.5 μg falls within the claimed dosage ranges thereby anticipating these ranges. These liquid compositions comprising T_3S are administered to rats via injection (p. 230, Experimental procedures). The liquid composition when administered *in vivo* to rats leads to no ill effects (see data Table 1, also Results). As the composition is in liquid form, it necessarily comprises a solvent and/or carrier and/or diluent.

As the composition of Chopra et al. contain all the requisite ingredients set forth by the claims, and are shown to be effective medicaments when administered in vivo, they would necessarily be able to carry out the claims' preamble limitation of being an oral composition for administration to a human. It is noted that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or

the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, there is nothing in the composition of Chopra et al. preventing its use orally in a human.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chopra et al. ("Demonstration of Thyromimetic Effects of 3,5,3'-Triiodothyronine Sulfate (T_3S) in Euthyroid Rats" Thyroid, 1996, 6(3), 229-232, as per Applicant's IDS dated 4/22/2005) in view of Miura et al. (US 5116828; of record).

The teachings of Chopra et al. are set forth above. In addition, Chopra et al. also teach that T_3S exhibits thyromimetic effects in hypothyroid rats and that on a molecular basis it is approximately one fifth (20%) as active as triiodothyronine (T_3) (p. 229, Introduction second full paragraph, also abstract). Chopra et al. teach that adult and fetal tissues contain sulfatase(s) which are capable of converting T_3S into T_3 (p. 230 final two sentences through p. 231 end of first partial paragraph). The thyromimetic effects of T_3S, which are observed in both euthyroid rats and in hypothyroid rats, is likely due to the generation of T_3 in tissues by desulfation of T_3S (abstract, p. 231 first column). T_3S exhibits the same potency as T_4 (thyroxine), which is also a source of T_3 (p. 231, first paragraph and first paragraph p. 229). The potency of both T_3S and T_4 is 20% of that of T_3. Chopra et al. also teach that treatments of T_3 and T_3S both caused a significant reduction in serum T_4 and TSH levels (abstract, Results p. 230).

The teachings of Chopra et al. differ from the instant claims in that the composition of Chopra et al. does not contain the requisite ingredient T_4 (thyroxine).

Miura et al. teach L-thyroxine (T_4) in doses of 25-400 μg/day, and L-triiodothyronine (T_3) in doses of 5-150 μg/day (col. 3, lines 1-4). These doses can be formulated for oral or parenteral administration and can contain common excipients, binders, disintegrators, lubricants, thickeners, wetting agents, buffers, solvents, oils, among others (col. 6, lines2-26). Miura et al. also teach that T_4 and T_3 are thyroid hormones (claim 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have formulated a composition comprising both T_3S in an amount from 5 to 1000 μg, or most specifically from 25 to 250 μg, as well as T_4 in an amount of 10 to 250 μg, or most specifically 25 to 200 μg with the reasonable expectation that such a composition would have thyromimetic effects. One would have been motivated to do so because both T_3S and T_4 produce the more active thyroid hormone T_3 in vivo. Both T_3S and T_4 are also known to exhibit thyromimetic effects. By these tokens they are functional equivalents. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). In the instant situation one of ordinary skill in the art would be imbued with the reasonable expectation that the combination of one thyromimetic with another would, when combined, result in a third composition also capable of exhibiting thyromimetic effects and in this case also producing the thyroid hormone T_3 upon administration.

One would be motivated to use 25 to 200 μg of T_4 because the prior art teaches that daily dosages of 25-400 μg are common dosages. This dosage range overlaps with the claimed dosage amounts. It is also well known in the pharmaceutical arts to adjust the relative dosage depending on the subject to be administered, the preparation form, route for administration etc. (Miura et al. col. 2, lines 32-44).

Claims 14-15 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chopra et al. ("Demonstration of Thyromimetic Effects of 3,5,3'-Triiodothyronine Sulfate (T_3S) in Euthyroid Rats" Thyroid, 1996, 6(3), 229-232, as per Applicant's IDS dated 4/22/2005) in view of Miura et al. (US 5116828; of record) in further view of Chiang et al. (US 2001/0051657).

The teachings of Chopra et al. and Miura et al. are set forth above. The combined teachings of Chopra et al. and Miura et al. fail to teach a kit as required by claims 14-15 and 25.

Chiang et al. teach kits useful for treating a variety of conditions including hypothyroidism comprising two different pharmaceutical compositions each useful at treating hypothyroidism as well as a container ([0139]-[0142]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have developed a kit comprising an oral composition comprising T_3S and a second composition comprising T_4, more specifically wherein the respective compositions comprise from 10 to 500 μg or 25 to 250 μg T_3S and from 10 to 250 μg or 25 to 200 μg T_4. One would have been motivated to do so because kits comprising two

different compositions for treating the same condition, including hypothyroidism, which both T_3S and T_4 are known to do, are well known in the prior art. One would be particularly motivated to add a second composition comprising T_4 since it is known that the administration of T_3S leads to low serum levels of T_4. One would add a T_4 composition to the kit in an effort to give the patient an opportunity to round out their thyroid hormone levels.

Response to arguments and 37 CFR 1.132 Declaration

Applicant's arguments filed 4/9/2010 regarding the rejection of claims have been fully considered, but are moot in light of the new grounds of rejection. However, in an effort to expedite prosecution, the Examiner will address any issues still relevant as well as the data presented in the declaration.

Applicant argues that the cited references, namely the Santini et al. reference (the rejection over this reference has been withdrawn) is exclusively directed to intraperitoneal injection of T_3S and not oral administration. Applicant argues that this difference prevents a prima facie case of obviousness from being established. This argument is not persuasive.

As addressed in the above rejections over Chopra et al., who also administers the T_3S composition intraperitoneally, there is nothing in this intraperitoneal composition which would prevent its use orally. As the composition of Chopra et al. contain all the requisite ingredients set forth by the claims, and are shown to be effective medicaments when administered in vivo, they would necessarily be able to carry out the claims'

preamble limitation of being an oral composition for administration to a human. It is noted that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Several of applicant's arguments are directed to the teachings of Lopresti. Applicants argue that Lopresti is the only cited reference which actually investigated the thyromimetic activity and metabolism of oral T_3S (albeit radiolabeled T_3S). Applicant argues that Lopresti shows that radiolabeled T_3S is an inactive metabolite which was presumably not absorbed by the GI system upon oral administration. The arguments surrounding Lopresti are unpersuasive.

The rejection over Lopresti was withdrawn in the Office action dated 10/22/2009. As addressed in this Office action, the rejection was withdrawn because one would not have been motivated to administer the instant claim's required dose of radiolabeled T_3S without inflicting undue harm to the subject. Again it is noted that the amount of radiolabeled T_3S is far smaller than the amount required by the instant claims or the amount administered in the currently applied prior art. Only 25 μCi of radiolabeled T_3S is administered (p. 704, second column, second to final full paragraph).[1] Accordingly,

[1] Given the fact that ^{125}I has a specific radioactivity of 75 GBq/μmol and 1 Ci = 3.7 x 10^{10} Bq and the molecular weight of T_3S of 729 g/mol, one can calculate that only 0.009 μg of radiolabeled T_3S was administered in Lopresti.

based on the dosage amount alone, one would not expect this small amount of radiolabeled T_3S to have an effect given the state of the prior art.

Applicant finally argues that the declaration shows that the claimed oral compositions have unexpected advantages over the cited prior art. Specifically, applicant argues that the declaration shows that the oral compositions of the invention were absorbed by the GI system and were metabolized to the active T_3 when administered to human subjects at doses of 20 to 160 μg T_3S. Applicant argues that this data is unexpected in view of the teachings of Lopresti. These arguments and the declaration are unpersuasive.

First, the teachings of Lopresti, as addressed above, are irrelevant given the relatively small amount of radiolabeled T_3S administered orally. More importantly, the prior art teaches that T_3S is known to be converted to the active T_3 upon in vivo administration due to the presence of sulfatases in adult and fetal tissues (Discussion p. 230). Accordingly the findings of the declaration support that which was shown in the prior art. "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). See also MPEP 716.02(c) II.

Conclusion

Claims 9-15 and 25 are rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 10 am to 7 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

/Ashwin Mehta/

Primary Examiner, Technology Center 1600